REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Nanomedicine Applications of Selenium Nanoparticles: Small is Big

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Abstract

Selenium (Se) is an essential micronutrient required for proper functioning of biological and metabolic mechanism within the human body. Deficiency of Se leads several harmful disorders such as cancer, neurological, muscular, immune, etc. Recently, selenium nanoparticles (SeNPs) attracted the interest of many researchers due to their biocompatibility, bioavailability, and low toxicity. Therefore, due to their higher bioactivity, SeNPs are largely being used in various biomedical applications. Generally, SeNPs can be synthesized by physical, chemical, and biological methods. However, the biologically synthesized SeNPs demonstrate greater compatibility with human organs and tissues. The effect of size, shape, and the method employed for their synthesis on their applications in biological systems has been explored by many researchers. This review highlights their applications in the biomedical field such as in the treatment of bacterial infections, cancer, and diabetes. They can also act as chemopreventive agents, anti-inflammatory agents, antiapoptotic and antioxidants.

Keywords: Selenium; Selenium nanoparticles (SeNPs); antioxidants; anti-inflammatory; anti-apoptotic.

1. Nanomedicine

Living systems are essentially comprised of building blocks which are nano–scaled **(Jayachadran et al., 2020)**. The science of suppressing, identifying, and managing diseases, traumatic injury, drug targeting, increasing bioavailability, analgesic effects, controlled drug release, improving human health, by using nano–scaled dimensions from 1.0 to 100.0 nm and taking benefits of exclusive properties of nano-scaled particles, is called nanomedicine **(Sarfaraz et al., 2018)**.

1.1. Nanoparticles (NPs)

Nanotechnology refers to an emerging field of science that includes synthesis and development of various nanomaterials. Nanoparticles (NPs) are particles of sizes ranging from 1 to 100 nm with one or more dimensions. The NPs are generally classified into organic, inorganic and carbon-based particles in nanometric scale. NPs have improved properties compared to larger sizes of respective materials and show enhanced properties such as high reactivity, strength, surface area, sensitivity, stability, etc. because of their small size **(Anu Mary Ealia and Saravanakumar, 2017)**. The main advantages of NPs are summarized in **Figure 1**.

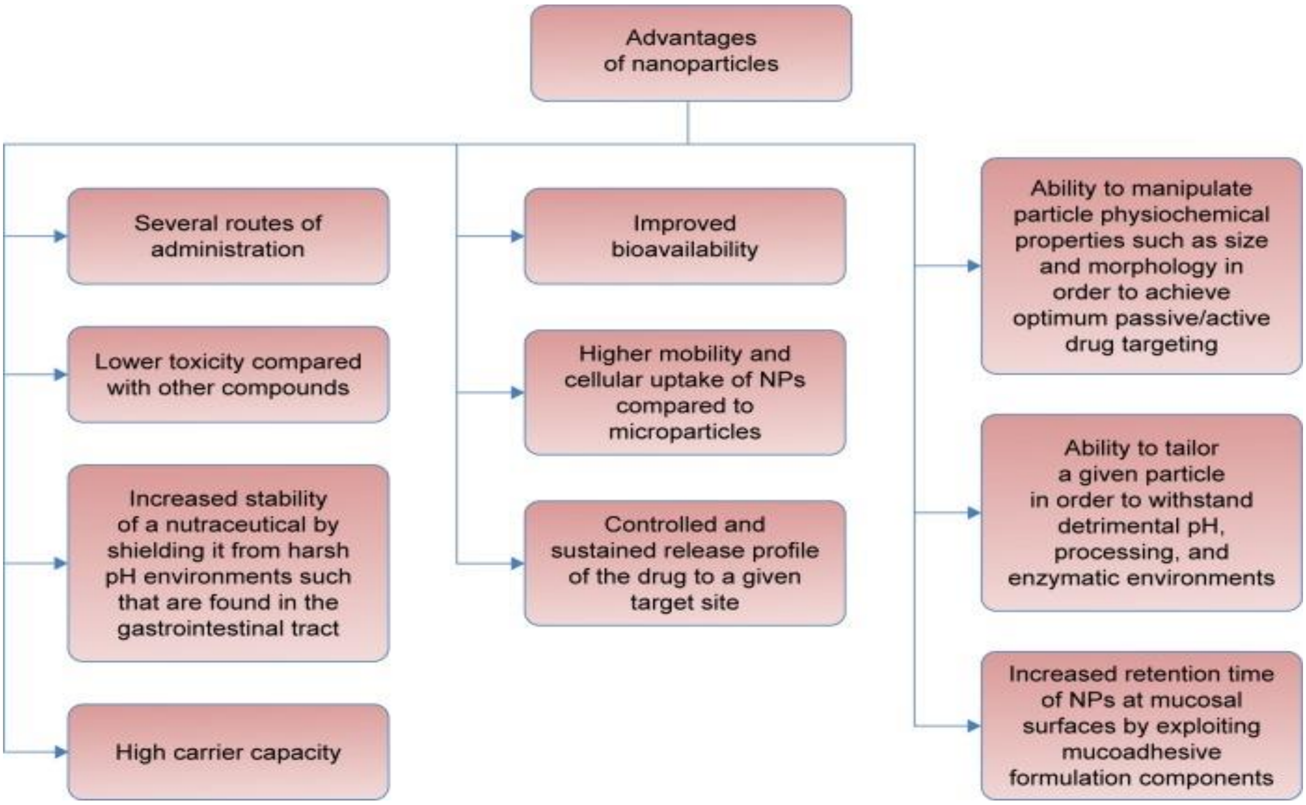

Figure 1. Diagram showing the main advantages of nanoparticles **(Hosnedlova et al., 2018)**.

1.1.1. Synthesis of NPs

The NPs are synthesized by various methods that are categorized into bottom-up or top-down method.

Bottom-up method

Bottom-up or constructive method is the build-up of material from atom to clusters to NPs. Sol-gel, spinning, chemical vapour deposition, pyrolysis and biosynthesis are the most used bottom-up methods for NPs production **(Anu Mary Ealia and Saravanakumar, 2017)**.

Top-down method

This method involves starting from larger molecule, which are decomposed into smaller units and then these units are converted into suitable NPs. Examples of this method are grinding/milling, physical vapor deposition and other decomposition techniques **(Iravani et al., 2014)**.

1.1.2. Mechanism of passage of NPs through intestinal mucosa

NPs pass through the intestinal epithelium in two ways: paracellular (between adjacent cells) or transcellular (through the cells) **(Figure 2)**. Under physiological conditions, the first way is restricted by a narrow region of intercellular spaces and by the tightness of the junctions between the epithelial cells (pore diameter is between 0.3 and 1.0 nm). Transcellular transport of NPs takes place through a process called transcytosis, which starts with endocytosis in the apical membrane of the cells. Subsequently, the NPs are transported through the cells and released on the basolateral pole **(Hosnedlova et al., 2018)**.

1.2. Nano-antioxidants

Nanoscale and supramolecular drug delivery systems have emerged as prominent methods to improve the pharmacological and therapeutic effects of many natural and synthetic drugs **(Doane and Burda., 2012)**. Antioxidants, due to their poor bioavailability and biocompatibility, can be encapsulated with nanomaterials to form nano-antioxidants to obtain the ideal solubility and permeability profile and to preserve the antioxidant from the probable enzymatic degradation. Furthermore, the modification of pharmacokinetics and tissue distribution properties as well as improving intracellular penetration and distribution of the targeted compound are among the advantages of nano-formulated antioxidants.

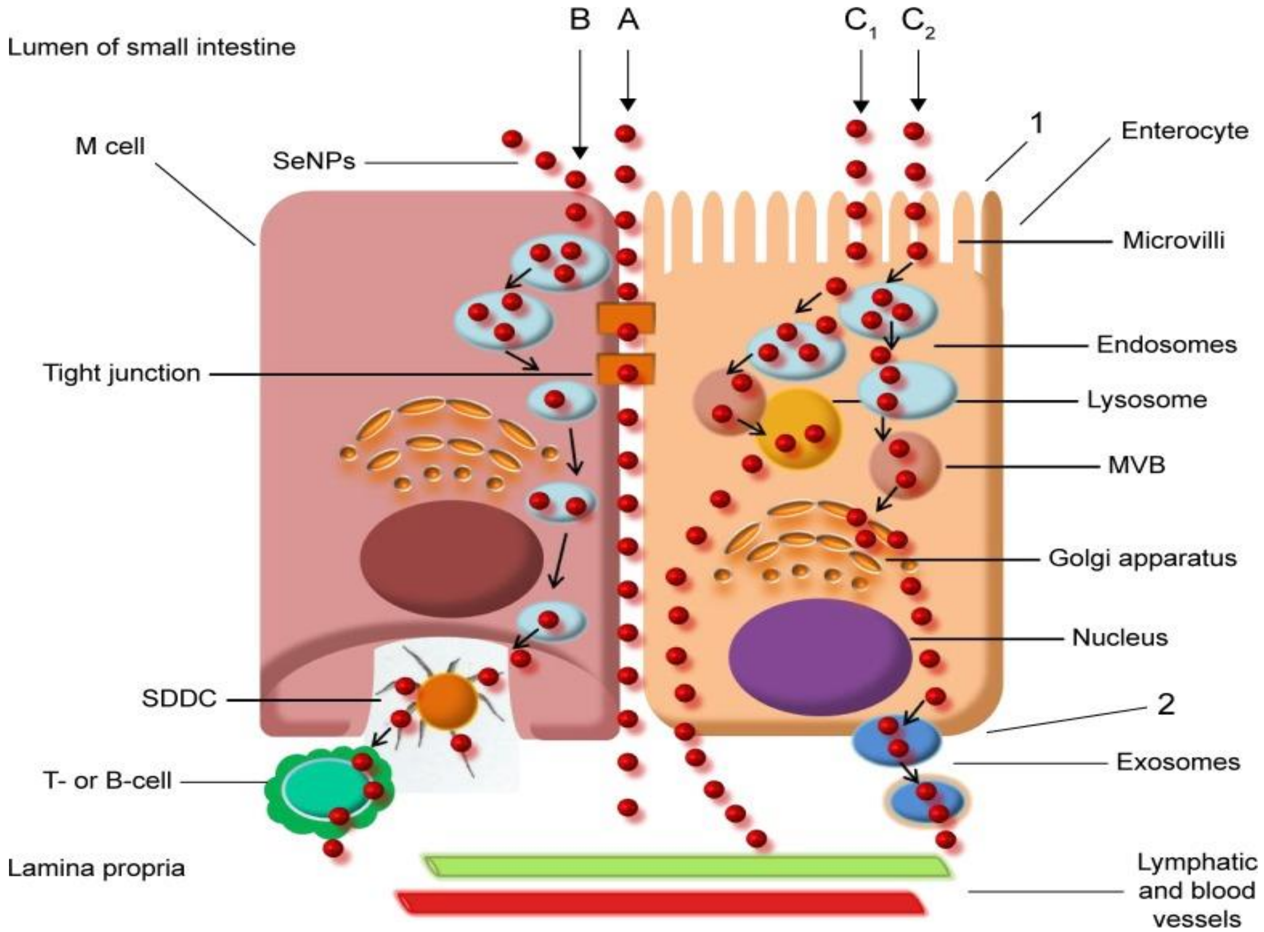

Figure 2. Diagram of nanoparticle transport across the intestinal mucosa of the small intestine **(Hosnedlova et al., 2018)**.

Environmental toxicants induce ROS formation that leads to lipid peroxidation, oxidative stress, glutathione depletion etc. They also affect intracellular compartments such as mitochondria. Nano-antioxidants prohibit this process due to their improved structure and functionality in comparison with antioxidants. The inhibitory effects of nano-antioxidants are illustrated in **Figure 3 (Eftekhari et al., 2018)**.

2. Selenium (Se)

Se is an essential micronutrient, whose trace amounts are essential for life. It constitutes an integral part of selenoproteins and some antioxidant enzymes. Se is incorporated as selenocysteine (SEC) in various antioxidant enzymes like glutathione peroxidase (GPX), thioredoxin reductase (TrxR) and selenoprotein P **(Kieliszek and Błażejak, 2016)**. Se acts as the redox center of all these enzymes and is essential for their biochemical activity. Some of the other important Se containing compounds are sodium selenite, selenomethionine and monomethylated Se which can act as anticancer agents (mainly chemopreventive) by different mechanisms **(Fernandes and Gandin, 2015)**.

As a component of some proteins, Se plays an important role in many disorders including cancer, cardiovascular, and kidney disease. The kidneys play a central role in the homeostasis of many small molecules and elements, including Se. In fact, the kidneys and thyroid gland have the highest Se concentration of all human organs **(Zachara, 2015)**.

Se is frequently used for therapeutic and protective purposes in animal models of experimentally induced nephrotoxicity. Various selenoproteins play an important role in antioxidant defense systems, and Se has anti-inflammatory and anti-apoptotic effects **(Sengul et al., 2021)**.

3. Selenium nanoparticles (SeNPs)

Traditional supplements of Se generally have a low degree of absorption and increased toxicity.

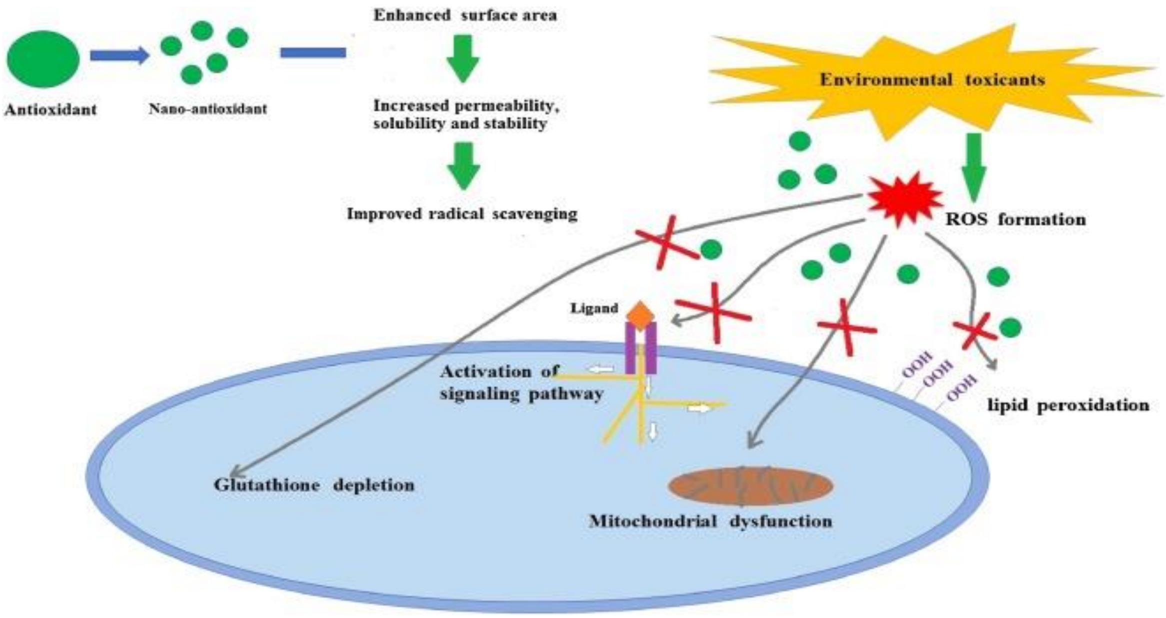

Figure 3. The promising effects of nano-antioxidant therapy against environmental pollutants induced-toxicities **(Eftekhari et al., 2018)**.

Therefore, it is imperative to develop innovative systems as transporters of Se compounds, which would raise the bioavailability of this element and allow its controlled release in the organism. Nanoscale Se has attracted a great interest as a food additive especially in individuals with Se deficiency, and as a therapeutic agent without significant side effects in medicine **(Hosnedlova et al., 2018)**.

SeNPs have picked up a vital prospect in the field of medical applications when compared to other selenium compounds, due to their excellent biological activities, better biocompatibility, and low toxicity **(Menon et al., 2018)**. Se has a narrow therapeutic window, and its toxicity margins are very delicate, whereas SeNPs possess remarkably reduced toxicity. SeNPs have been explored in various oxidative stress and inflammation mediated disorders like arthritis, cancer, diabetes and nephropathy with potential therapeutic benefits. SeNPs constitute an attractive carrier platform to ferry various drugs to the site of action **(Khurana et al., 2019)**.

3.1. SeNPs as antioxidant and anti-inflammatory agents

SeNPs have attracted increasing attention in the past due to their antioxidant activities and low toxicity. Several studies showed that SeNPs have anti-oxidant activities both *in vitro* and *in vivo* through the activation of selenoenzymes such as glutathione peroxidase (GPx) and and thioredoxin reductase (TrxR) which prevent oxidative damage to body tissues **(Abd El-Moneim et al., 2018)**. The free radical scavenging capacity of SeNPs could be due to their ability to penetrate cells easily and inhibit reactive oxygen species (ROS) production and thereby inhibiting the free radical chain reactions resulting in improvement of the antioxidant defense mechanisms **(Dahdouh et al., 2019; Mehanna et al., 2022)**. In addition, several studies have focused on the ameliorative effect of SeNPs on different organs, such as the brain. They showed neuroprotective activity against stroke in murine models owing to their high antioxidant and neuroprotective properties **(Yuan et al., 2020)**.

Treatment with SeNPs reduced testicular levels of NO in streptozotocin (STZ) diabetic rats **(Dkhil et al., 2016)**. Additionally, anti-inflammatory properties of SeNPs were investigated against murine Raw 264.7 macrophage cells induced by lipopolysaccharides (LPS), where they managed to inhibit NO production and downregulate iNOS expression **(Wang et al., 2014)**. Also, SeNPs exhibited a protective and anti-inflammatory effect against bleomycin-induced pulmonary injury in male rats. SeNPs improved the degree of alveolitis and inflammation and lung structure damage, and led to significant decreases in density of transforming growth factor- β1 (TGF-β1) and tumor necrosis factor-α (TNF-α) **(Shahabi et al., 2021)**. Treatment with SeNPs decreased serum kidney injury molecule-1 (KIM-1) levels in glycerol-induced acute kidney injury in rats **(AlBasher et al., 2020)** and attenuated the levels of TNF-α in several models of experimentally induced inflammation **(El-Ghazaly et al., 2017; Ali et al., 2020; Shahabi et al., 2021)**.

3.2.Antiapoptotic effect of SeNPs

Apoptosis plays a central role in many inflammatory diseases. Apoptosis refers to the autonomous and orderly process of cell death controlled by genes to maintain the stability of the internal environment. It involves the activation, expression, and regulation of a series of genes including Bcl-2 family, caspase family, oncogenes, etc. Among these various genes, caspase family is a protein system that directly leads to the disintegration of apoptotic cells and plays an important role in maintaining homeostasis **(Ashkenazi et al., 2017)**.

SeNPs inhibit apoptosis through their ability to modulate the expression of Bcl-2 and Bax, decreasing the ratio of Bax/Bcl-2, the main index for apoptosis (Saif-Elnasr et al., 2019). This, in turn, provides evidence for the anti-apoptotic properties of SeNPs **(Li et al., 2021)**. Se deficiency was found to aggravate caspase-3 dependent apoptosis induced by H_2O_2 in cultured pig thyroid cells, and this was related to the impaired capacity of GPx in deficiency of Se **(Demelash et al., 2004)**. More recently, biofunctionalized SeNPs showed a protective effect against H2O2 induced apoptosis through decreasing intracellular ROS production, ameliorating mitochondrial damage and inhibiting caspase-3, caspase-8, and caspase-9 (**Wang et al., 2019)**.

3.3. Potential applications of SeNPs

SeNPs can play a role in many physiological processes like growth, reproduction, and immunomodulation which are important for the survival of human beings **(Hosnedlova et al., 2018)**. Nowadays, SeNPs have wide applications in medical diagnostics and drug delivery systems. Since SeNPs show much lower risk compared to Se, they have been widely used as antioxidant, dietary supplement, antimicrobial **(Geoffrion et al., 2020; Menon et al., 2020)**, anticancer **(Zeng et al., 2019)**, and antidiabetic agents **(Zeng et al., 2018)**.

SeNPs are preferred over other forms of Se in treatment of diseases like cancer, muscular dystrophy, diabetes, liver fibrosis, bacterial and fungal diseases, etc. **(Khurana et al., 2019)**. Also, SeNPs are used in the treatment of heavy metal and chemical toxicity due to their antagonistic effect against these materials. Similarly, SeNPs antagonize the cadmium chloride-induced neurotoxicity and nephrotoxicity in rats **(Sadek et al., 2017)**. They also showed an antagonistic effect against vancomycin induced nephrotoxicity by minimizing oxidative stress, apoptosis and cellular damage in kidney tissue of experimental rats **(Mehanna et al., 2022)**. Similarly, SeNPs were reported to have a preventive effect on hexavalent chromium induced thyrotoxicityand abnormal liver metabolism **(Luo et al., 2019)**.

3.3.1. Anticancer effects of SeNPs

Cancer is one of the most devastating disorders of the 21st century, creating a major concern among clinicians and researchers. The ever-growing problem of drug induced toxicity and resistance has doubled the trouble. Many different treatment strategies are being tried to fight the war against cancer and a plethora of strategies have been attempted. Nanotechnology has significantly improved our approach of personalized medicine whereby the targeting has improved and at the same time the toxicity can be suppressed. Nowadays, SeNPs are widely being investigated for their anti-cancer activity against breast, lung, kidney, and osteosarcoma cancers based on *in vivo* and *in vitro* experiments. SeNPs have an anticancer effect as they increase cell apoptosis. Numerous researchers reported the anticancer effect of SeNPs (**Gandin et al., 2018)**.

Arabinogalactans stabilized SeNPs showed an inhibitory effect on MCF-7, A549, and HepG-2 cells by increasing cellular apoptosis **(Tang et al., 2019)**. SeNPs conjugated with ferulic acid (FA-SeNPs) had an anticancer effect on HepG-2 cells **(Cui et al., 2018)**. SeNPs functionalized liposomes in conjugation with doxorubicin showed an increase in the anticancer activity **(Xie et al., 2018)**. Selenium-curcumin nanoparticle (SeCurNPs) showed an anticancer effect on colorectal carcinoma (HCT116) and Ehrlich's ascites carcinoma cells **(Kumari et al., 2017)**. The combination of SeNPs with irinotecan (an anticancer drug) increased anticancer effect against HCT-8 cells by enhancing p53 arbitrated apoptosis.

Thus, SeNPs combined with anticancer drugs can be used for cancer treatment due to their bioavailability and low toxicity towards normal cells but high toxicity for cancer cells **(Baskar et al., 2019)**.

3.3.2. Antidiabetic effect of SeNPs

Diabetic patients share several pathological features comprising inflammation and oxidative stress. Owing to the efficient anti-inflammatory and antioxidant actions of Se, several studies revealed the link between diabetes mellitus and serum level of Se. Previous studies have shown that the higher Se level is linked with a lower risk of type 2 diabetes mellitus (T2DM) development. Interestingly, SeNPs have an intrinsic hypoglycemic effect beside their antioxidant and anti-inflammatory activities. SeNPs can be used in management of T1DM and T2DM through alleviation of oxidative stress and sensitizing insulin **(Abdulmalek and Balbaa, 2019)**.

Vasoactive intestinal peptide receptor 2 (VPAC2) agonist peptide-conjugated chitosan modified SeNPs were found to show selective activity against type-2 diabetes. The NPs were reported to enhance proliferation, glucose uptake and insulin uptake along with reduction in intracellular oxidative stress. In a recent breakthrough, SeNPs were proposed as a plausible vehicle for oral delivery of insulin. The NPs were reported to have synergistic antidiabetic activity with promising antioxidant, improved pancreatic islet function and promoted glucose utilization. Anti-diabetic activity of SeNPs is illustrated in figure 4 **(Deng et al., 2017)**.

3.3.3. Antibacterial effect of SeNPs

Living beings are susceptible to microbial infections leading to numerous diseases causing great health concerns. Nowadays, most of the pathogenic organisms have become drug-resistant because of the constant utilization of a wide range of antibiotics. Particularly, multidrug-resistant microorganisms and fungi are profoundly becoming irresistible as they have procured protection from practically all the accessible antimicrobial drugs. Therefore, anti-infection agents are developed for the treatment of these irresistible diseases. Generally, SeNPs have size and concentration dependent effects against various microorganisms. Further, they exhibit antimicrobial activity and destruction of biofilm formation. These nanoparticles were effective on inhibiting the growth of *E. coli* JM109, *Pseudomonas aeruginosa* PAO1, and *S. aureus* ATCC 25923. Consequently, SeNPs can be utilized as an effective antimicrobial agent in pharmaceutical applications **(Bisht et al., 2022)**.

The advantage of using SeNPs as an antibacterial agent is that they are target-specific, highly biocompatible, highly reactive, and have a high surface area to volume ratio. It is assumed that they can permeate through the cell membrane via endocytosis and damage the genetic components of bacterial cells **(Menon et al., 2020)**.

3.3.4. Antifungal effect of SeNPs

SeNPs acquire antifungal properties for various biological applications. To name a few, SeNPs can be used for the treatment of fungal infections in immunity compromised patients, improvement in

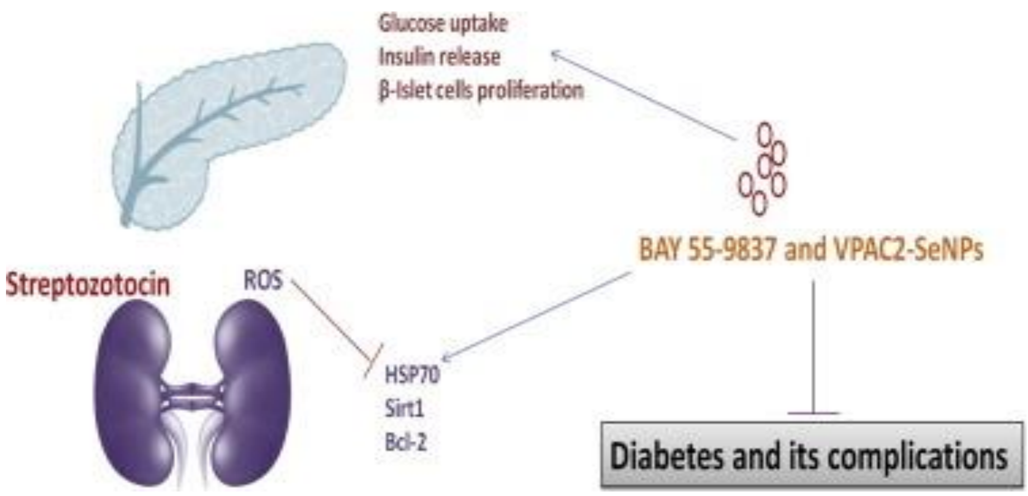

Figure 4. Anti-diabetic activity of SeNPs **(Deng et al., 2017)**.

probiotic concentration, and fabrication of antifungal and antibacterial cloths for protecting skin from S. aureus and Tinea pedis infections. SeNPs can provide antifungal activity in patients having less immunity against nystatin-immune Candida sp. and a more constructive therapy to encounter intrusive aspergillosis in comparison to the amphotericin B drug. Nano-Se modified with biogenic polysaccharide–protein (PSP) complexes collected from Pleurotus tuber-regium deposited on a fabric was effective in inhibiting the growth of S. aureus and Trichophyton rubrum bacteria **(Bisht et al., 2022)**.

4. Conclusion

In conclusion, the biological properties of nano-sized Se have a beneficial role in nanomedicine and biomedicine applications. SeNPs have high bioavailability and low toxicity. The incorporation of Se into NPs has emerged as a promising approach to harness both the therapeutic benefits of Se and the unique properties of NPs. Several studies showed that SeNPs are excellent in combating fatal diseases like cancer, diabetes, drug-induced toxicity.

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